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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/731,905
Filing Date: December 10, 2003
Appellants: KOPPIKER ET AL.

A. Dean Olson
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed February 12, 2007 appealing from the Office action mailed April 10, 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The Appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct.

The Examiner does not dispute that the when the claimed cyclic-3',5-guanosine monophosphate, ("cGMP") phosphodiesterase isoform type 5, ("PDE5") is in combination with pregabalin or gabapentin, as well as a pharmaceutically acceptable excipient, diluent or carrier, and when such combination is employed in a method of treating diabetic neuropathy which includes a step of administering such combination to a patient in need thereof a medical benefit is realized.

However, the Examiner disputes Appellant's characterization of such claimed subject matter as providing a "significant" medical benefit, (brief at page 3, third line from the bottom of the page), to the extent that "significant" may be interpreted as meaning that the claimed subject matter provides benefits above that which would have been reasonably expected by one of ordinary skill in the art to which said subject matter pertains at the time the invention was made.

(6) Grounds of Rejection to be Reviewed on Appeal

The Appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,166,219	YAMASAKI et al.	12-2000
6,127,418	BUENO et al.	10-2000
WO 94/28902	ELLIS et al.	12-1994
WO 98/03167	SINGH	01-1998

Stedman's Medical Dictionary, 22nd Edition, published 1972 by The Williams & Wilkins Company, (Baltimore), pg. 1000, "polyneuropathy".

(9) Grounds of Rejection

The following ground of rejection are applicable to the appealed claims:

Claims 17-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamasaki et al. (U.S. Patent No. 6,166,219; Issued December 2000, Filed November 1998) in view of Ellis et al. (WO 94/28902; 1994), Singh (WO 98/03167; 1998), Bueno et al. (U.S. Patent No. 6,127,418; Issued October 2000, Filed April 1999) and Stedman's Medical Dictionary (Twenty-Second Edition; 1972).

Yamasaki et al. teaches a pharmaceutical composition comprising a cGMP PDE5 inhibiting benzimidazole compound of the formula (I) or a pharmaceutically acceptable salt thereof (col.35, line 64 - col.36, line 26) in combination with a pharmaceutically acceptable carrier (col.37, line 65 - col.38, line 6) and further teaches a method of treating a disorder that is responsive to treatment with a cGMP PDE5 inhibiting compound by administering an effective amount of a cGMP-PDE inhibiting compound of formula (I) or a pharmaceutically acceptable salt thereof (col.35, lines 22-55) in a variable amount depending on the age, condition and type of disorder of the patient to be treated (col.38, lines 16-20). The disclosed composition can be

administered orally in the solid form of tablets, granules, powders or capsules or in liquid forms, such as solutions, suspensions, syrups, emulsions or "lemonades" (col.37, line 65-col.38, line 9). Yamasaki et al. further teaches various medical conditions which are responsive to treatment with the cGMP PDE5 inhibiting compounds, including diabetic neuropathy (col. 1, lines 14-44, especially line 21).

It is acknowledged that Yamasaki et al. is silent as to the particular IC50 concentration or the selectivity ratio of the inhibitor. However, in light of the fact that the particular type of compounds presently claimed are expressly disclosed in Yamasaki et al. and are recognized to function in the same manner as required by the present claims (col.35, lines 22-55, especially lines 52-53), the IC50 concentration or the selectivity ratio of the inhibitor are not seen to differ between the prior art of Yamasaki et al. and that of the present claims, absent factual evidence to the contrary (see present claims 19-20, 24-25 and 30-31).

The differences between the Yamasaki et al. reference and the presently claimed subject matter lie in that the reference does not teach:

(i) the concomitant administration of gabapentin or pregabalin with the cGMP PDE5 inhibitor or the formulation of gabapentin or pregabalin in combination with the cGMP PDE5 inhibitor in the pharmaceutical composition (see present claims 17, 18, 22, 23, 27, 33 and 34);

(ii) the particular use of sildenafil or its pharmaceutically acceptable salts as the cGMP PDE5 inhibitor (see present claims 21 and 32); and

(iii) the treatment of diabetic polyneuropathy (see present claim 28).

However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains because:

(i) It is acknowledged that Yamasaki et al. is silent as to the use of gabapentin or pregabalin in the disclosed composition administered for the treatment of diabetic neuropathy. However, both gabapentin and pregabalin were well known in the art to be useful for the same therapeutic purpose of treating diabetic neuropathy. Singh discloses the use of gabapentin or (S)-3-(aminomethyl)-5-methylhexanoic acid (also known as pregabalin; see Bueno et al., U.S. Patent No. 6,127,418, at col.2, lines 50-55) for the treatment of diabetic neuropathy and further discloses a pharmaceutical composition comprising the active GABA analogue compound in combination with an inert, pharmaceutically acceptable carrier for oral administration to mammals, including humans, suffering from such a condition by administering an effective amount of the compound (page 5, lines 9-19 and page 7, lines 4-20). It would, therefor, have been obvious to a person of ordinary skill in the art to employ either gabapentin or pregabalin in combination with a cGMP PDE5 inhibiting composition as disclosed by Yamasaki et al. because each compound was known in the art to be successful for achieving the same therapeutic effect.

Motivation to administer both compounds flows logically from the efficacy of each compound in treating diabetic neuropathy as demonstrated in the prior art and further, because each compound has been previously administered for this same therapeutic objective, at least additive results would have been desired and expected. In the absence of evidence to the contrary, it is generally *prima facie* obvious to use in combination two or more agents that have previously been used separately for the same purpose. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) and MPEP § 2144.06.

(ii) It is acknowledged that Yamasaki et al. do not expressly teach the use of the cGMP PDE5 inhibitor sildenafil, or its pharmaceutically acceptable salts thereof, as a compound for treating diabetic neuropathy. However, Yamasaki et al. discloses that diabetic neuropathy is a condition responsive to treatment with a cGMP PDE, particularly a cGMP PDE5, inhibiting compound. In light of such a relationship, it would have been an obvious conclusion to one of ordinary skill in the art that the treatment of a condition known to be responsive to a cGMP PDE5 inhibiting agent would not be solely limited to those compounds disclosed by Yamasaki et al, but that effective treatment of such a condition would have been reasonably expected to occur with any one or more other compounds known to exert the same effect (i.e., the inhibition of cGMP PDE5). Thus, the use of any cGMP PDE5 inhibitor compound, such as sildenafil, for the formulation of a pharmaceutical composition administered for the treatment of diabetic neuropathy would have been obvious to, and a matter well within the purview of, one of ordinary skill in the medical art. Ellis et al. teaches the compound 5-[2-ethoxy-5-(4-methyl-l-piperazinylsulphonyl)-phenyl]-l-methyl-3-n-propyl-l,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one as a potent and selective inhibitor of cGMP-specific PDE5 (page 7, lines 1-3 and page 9, lines 1-3 of the last paragraph). 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one is also known as sildenafil (see Appellants' disclosure at page 1, lines 12-13).

The use of such a compound was well known in the art to exert inhibitory effects on cGMP-PDE5 and, therefore, would have been reasonably expected to demonstrate the same, or substantially similar, efficacy in treating diabetic neuropathy, as that shown by the benzimidazole cGMP-PDE inhibiting compounds expressly taught by Yamasaki et al.

(iii) Although the present claims recite these of a cGMP PDE5 inhibitor compound in combination with gabapentin or pregabalin for the treatment of diabetic polyneuropathy, while the cited references teach diabetic neuropathy, the distinction between diabetic polyneuropathy and diabetic neuropathy is not considered a patentable difference, absent factual evidence or direction to the contrary. The presence of the prefix "poly" amounts to nothing more than a quantification of the number of peripheral nerves that are affected by neuropathy resulting from diabetes. In this regard, Stedman's Medical Dictionary has been cited (1972; p.1000) to show that polyneuropathy is defined as "a disease process involving a number of peripheral nerves." Thus, regardless of whether the neuropathic phenomenon affects one or more than one peripheral nerve(s), such does not change the fact that both cGMP PDE5 inhibitor compounds and gabapentin and pregabalin were known in the art for the treatment of diabetic neuropathy, in general. It would logically follow, therefore, that two compounds known to have efficacy in the treatment of diabetic neuropathy occurring in one nerve would also be reasonably suggestive of having efficacy in treating diabetic neuropathy occurring in multiple nerves.

(10) Response to Argument

Appellants' traverse of the present rejection at pages 5-21 of their brief has been carefully considered, but fails to persuade the Examiner of error in the determination of obviousness for the reasons set forth below, as well as those set forth in the final Office action dated April 10, 2006, pages 3-10, which reasons are here incorporated by reference.

Appellants' traverse is based on their belief that the Examiner has made 4 errors in rejecting the present claims. The following addresses the 4 supposed errors in the Examiner's conclusion of obviousness.

(A) As the first alleged error, Appellants set forth that "[T]he Examiner appears to be stating that the Yamasaki et al. benzimidazole compounds are cGMP PDE inhibitors and that they are stated to be useful for the treatment of diabetic neuropathy, and accordingly, all cGMP PDE5 inhibitors are useful for the treatment of diabetic neuropathy", (emphasis added, brief at page 7, second paragraph; see also the brief at pages 8-13, the section headed "D. Yamasaki et al. Does Not State that Diabetic Neuropathy May Be Treated Based On CGMP PDE5 Activity").

While the Examiner has not expressly stated the above on the record, Appellants are absolutely correct that the Examiner's premise is that any compound possessing cGMP PDE5 inhibitory activity should be useful for the treatment of diabetic neuropathy. This position is based on the teachings in Yamasaki et al. that diabetic neuropathy may be treated "based on" the cGMP PDE5 inhibitory activity of their disclosed benzimidazole compounds, (Yamasaki et al. at col 35, lines 27 and 52-55). The expression "based on" is clearly contrary to Appellants' position, clearly provides a clear nexus between the compounds' efficacy in treating diabetic neuropathy and the compounds' ability to inhibit cGMP PDE5 activity, i.e., the only cGMP PDE5 isoform identified by Yamasaki et al. That cGMP PDE5 inhibitors, as a class, would have been expected to be useful for treating diabetic neuropathy is germane insofar as, as noted in the statement of rejection, Ellis et al. teach sildenafil as cGMP PDE5 inhibitor and, as such, it would have been an obvious addition to the treatment regimen of Yamasaki et al.

In order to buttress Appellants' position that the claimed subject matter would not have been obvious, Appellants could have shown exceptions to the Examiner's premise by pointing to compounds which were known as cGMP PDE5 inhibitors, but which were not, in fact, effective for the treatment of diabetic neuropathy. If so established, the propriety of the present, tacit

conclusion that all cGMP PDE5 inhibitors are effective against diabetic neuropathy would be diminished thus requiring a new evaluation of the claimed subject matter under 35 U.S.C. § 103.

Appellants, however, have not done this. Rather, Appellants have offered that "Yet it is clear that the treatment of diabetic neuropathy by the benzimidazole compounds could be mediated by some other listed mechanism of action(s), (e.g., smooth muscle relaxing activity, bronchodilating activity, vasodilating activity, smooth muscle cell suppressing activity or yet another cGMP PDE isoform)", (brief at page 7, first paragraph).

This is not persuasive of error because the cGMP PDE5 inhibition is a *biochemical* mechanism of action and the other listed actions, i.e., smooth muscle relaxing activity, bronchodilating activity, vasodilating activity, smooth muscle cell suppressing activity, are physiological functions. This is significant because the artisan would have readily recognized that the physiological functions occurred because cGMP PDE5 was inhibited. Regarding the "or yet another cGMP PDE5 isoform" referenced by Appellants, Yamasaki et al. is silent as to any isoform of cGMP PDE other than the type-5 isoform. Accordingly, contrary to Appellants' opinion, the Examiner cannot be charged with the supposed error alleged by Appellants.

(B) The second supposed error in the Examiner's position is that "Yamasaki et al.'s teachings cannot be bridged by the Examiner reliance on anticipation law (which is not appropriate in an obviousness determination) and both the MPEP § 2131.02 and *Ex Parte A* address anticipation and not obviousness"; (brief at page 7, third paragraph and the section headed "Reliance On Anticipation Law Is Misplaced In This Obviousness Determination" at page 13).

The above position appears to be prompted by remarks of the Examiner in finally rejecting the claims. In particular, in their response to the Examiner's rejection in the Office action dated September 8, 2005, which has been reproduced above, Appellants' offered their concern that because Yamasaki et al. listed so many and various diseases/conditions, (*e.g.*, at col. 35, lines 22-51), this comprehensive listing would have somehow obscured the treatment of anyone of these diseases/conditions, such as diabetic neuropathy, from one of ordinary skill in the art.

In response, it is believed that rather than being a hindrance to the practice of the subject matter disclosed by Yamasaki et al., the comprehensiveness of the listing of diseases/conditions would have aided the artisan in identifying the full, or almost full, listing of the diseases which are amenable to treatment using the benzimidazole compounds disclosed by the patentees.

The Examiner further offered a legal rationale for showing Appellants that the comprehensiveness of the teachings of Yamasaki et al. did not diminish a conclusion that the treatment of any one of the diseases/conditions, such as diabetic neuropathy, would have been *prima facie* obvious. In particular, it was set forth:

> "The Examiner is guided in his opinion by MPEP § 2131.02 under the heading 'A Reference That Clearly Names The Claimed Species Anticipates The Claim No Matter How Many Other Species Are Named', where it is set forth: 'A genus does not always anticipate a claim to a species within the genus. However, when the species is clearly named, the species claim is anticipated no matter how many other species are additionally named. *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990) (The claimed compound was named in a reference which also disclosed 45 other compounds. The Board held that the comprehensiveness of the listing did not negate the fact that the compound

> claimed was specifically taught. The Board compared the facts to the situation in which the compound was found in the Merck Index, saying that 'the tenth edition of the Merck Index **lists ten thousand compounds**. In our view, **each and every one of those compounds is described**' as that term is used in 35 U.S.C. § 102(a), in that publication.'). *Id.* at 1718. See also *In re Sivaramakrishnan*, 673 F.2d 1383, 213 USPQ 441 (CCPA 1982)', (emphasis added). Accordingly, Applicants' position is without merit or germane to the instant issue of obviousness.", (final Office action at page 5).

It is correct that both MPEP § 2131.02 and *Ex Parte A* address an issue of anticipation. However, given that anticipation is the epitome of obviousness, the Examiner's reliance on anticipation law is not misplaced or in error.

(C) The third supposed error in the Examiner's rejection is that "the rejection is contrary to the law of obviousness" and only supports a conclusion that the claimed subject matter would have been "obvious to try", (see the brief at page 8, the third paragraph and at pages 13-17 under the heading "The Examiner's Rejection Is Contrary To The Law Of Obviousness – At Best This Is A Classic Case Of 'Obvious To Try'").

The Examiner agrees with Appellants that 'obvious to try' is not the standard for obviousness. Therefore, the Examiner has not based the instant conclusion of obvious on such standard. Rather, the Examiner has established that the presently claimed subject matter would have been "obvious to do".

As set forth under MPEP § 2145(X)(B), it is noted that "[t]he admonition that 'obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art

gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.... In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.' *In re O 'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)".

The Examiner's position, in contrast to Appellants', is that the differences between the claimed subject matter and that of the prior art are not such that there are numerous possible choices, (see MPEP § 2131.02 relied on above) or where there is a new technology to explore. The art relied on, as well as the Examiner's assessment of such art, makes it clear that it would have been "obvious to do" what Appellants are claiming. The treatment of diabetic neuropathy, as well as each and every other of the clearly named diseases/conditions would have been obvious, if not placed in possession of the public, because each diseases/condition is clearly named by the patentees. Also, because it is clearly disclosed that the compounds may be used based on the cGMP-PDE5 mechanism of action, it cannot be agreed, as urged by Appellants, that such amounts to an invitation to explore a new technology or general approach that seemed to be a promising filed of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. It is submitted that the teachings of Yamasaki et al are clear in this respect and direct the artisan, not to try, but to do, with a reasonable expectation of success, that which the patentees clearly disclose, including the treatment of diabetic neuropathy with a compound possessing the ability to inhibit cGMP-PDE5.

Appellants' focus on the blood-sugar reducing function of the compounds, (brief at

page 15, final paragraph, for example), is noted but is not seen to diminish the instant conclusion of obviousness as it is not in conflict with the cGMP PDE5 activity of the compounds disclosed in Yamasaki et al. In particular, it is not believed contrary to the treatment of diabetic neuralgia when blood sugar is reduced in a patient who suffers from a disease, i.e., diabetes, that is defined in-part by abnormal blood-sugar concentrations.

Appellants have set forth that the artisan would not have had a reasonable expectation of success, even if the art is, *arguendo*, viewed as providing a suggestion, In support of this position, Appellants have repeated their previous position that the Yamasaki reference only provides an invitation to experiment, "i.e., to perhaps making testing PDEV inhibitors more obvious to try, which again is manifestly not the proper standard for patentability"(brief at page 16, first full paragraph). However, insofar as the teachings of Yamasaki et al. are clear and would have been understood by one of ordinary skill in the art to use PDEV inhibitors for the purposes taught therein, it is maintained that the teachings of the reference are sufficient to base a proper conclusion of obviousness upon.

Appellants have also argued that rather than *In re Kerkhoven, In re Geiger*, 2 USPQ2d 1276 (Fed. Cir. 1987) is controlling, (brief at pages 16, second paragraph – page 17, first full paragraph). Here, however, unlike in *Geiger*, the reference was not as specifically detailed as Yamasaki et al. Short of anticipating the use of the claimed PDEV inhibitor, it is believed that the clear teaching of "***based on*** their [the disclosed benzimidazole compounds] cGMP-PDE (especially PDE-V)-inhibiting activity, smooth muscle relaxing activity, bronchodilating activity, vasodilating activity, smooth muscle cell suppressing activity and antiallergic activity", (emphasis added; col. 35, lines 52-55) provides one of ordinary skill in the art with the

reasonable expectation and motivation to employ other compounds possessing the same function and to reasonably expect the same results to occur as in Yamasaki et al. Further supporting the position of the Examiner is the MPEP at § 2144.06 where "Art Recognized Equivalence for the Same Purpose" is discussed, and in particular, the "substituting equivalents known for the same purpose". The present rejection is fully consistent therewith and therefore the Examiner is compelled to maintain the rejection to be proper.

(D) According to Appellants, the fourth error that the Examiner made was erroneously refuting Appellants' March 6, 2006 Response., (received and entered by the Office on March 9, 2006). In said response, Appellants remarked that their invention was even more unobvious than *Geiger* because "an alpha 2 delta compound ligand and a PDE V inhibitor are different drugs used for different purposes functioning by different mechanisms (which further confounds the ability to guess at their effects if combined)", (Appellants' amendment entered March 9, 2007 at page 13, towards the end of the second paragraph).

In response, the Examiner maintains that just because an alpha 2 delta compound ligand, (i.e., gabapentin), and the PDEV inhibitors have different functions, such does not diminish the merit of the present conclusion of obviousness . Both were well known in the art to function as treatments for diabetic neuropathies. Also, that two more compounds, used together, may have different mechanisms of action is not very impressive of an argument against such use or combination because if this were true, than it would have to also be true that it would always have been *prima facie* unobvious to use two or more drugs in combination for a given purpose where each drug was known to be useful for that purpose unless it was further taught that each

drug possessed the same mechanism of action, (emphasis added; final rejection dated April 10, 2006 at page 8, second paragraph).

On appeal, Appellants characterize the above Examiner's response as "simply incorrect", (brief at page 8, first paragraph). Appellants have not, however, provided a reason for their contention, i.e., by included a statement such as "The Examiner's response is simply incorrect because...". Rather, Appellants have only averred that drug-drug interactions are unpredictable which is "an important aspect of the lack of a reasonable expectation of success of Appellants' drug combination", (brief at page 8, first paragraph and page 18).

Appellants have not established that the Examiner's remarks, *supra*, are erroneous. The Examiner accepts that (i) drug-drug interactions were known in the art and that (ii) some drug-drug interactions were recognized to be dangerous such that the artisan would rarely, if ever, consider such drug-drug combination in therapy. However, Appellants' have not explained why one of ordinary skill in the art would have found or reasonably expected the presently claimed combination(s) to be so dangerous so as to not have employed the claimed combination for the purpose of treating diabetic neuropathy.

At page 18 of the brief, first paragraph, Appellants state that the Examiner's rejection includes reasoning that "oversimplifies the combination of pharmaceutical agents". To the contrary, it is believed that Appellants are overcomplicating the combination of the present active agents. The Examiner's position is not founded on the premise that it would have been obvious to combine *any and all* active agents in order to form a third composition that would be useful for the same purpose as each of the individual actives. Rather, based on the specific teachings in the art of record, it has been correctly reasoned that because the cGMP PDE5

inhibitors and gabapentin and/or pregablin are each known to be useful for the same function, i.e., treating diabetic neuropathy, one of ordinary skill in the art would have been motivated to combine such compounds to form a third composition that is also useful for treating diabetic neuropathy with the idea for combining them flowing logically from their having been used previously for the same purpose.

Further to their position on the unpredictability of drug-drug interactions and how such unpredictability would result in a lack of a reasonable expectation in doing what Appellants are claiming to do, Appellants state that combining actives should be counterbalanced against the possibility of improved patient compliance and there are many reasons why those skilled in the art would not pursue a particular combination. In support of their position on unpredictability, Appellants point to the specific example of the combination drug "PHEN-PHEN", i.e., a combination of phentermine and fenfluramine, that was found to produce dangerous effects in some patients and was removed from the drug market, (brief at page 18, first paragraph).

Appellants also point to Chapter 105 of "Remington: The Science and Practice of Pharmacy", 19th edition, (Drug Interactions, by DA Hussar), pages 1822 –1836), (brief at page 18, second paragraph). This reference has **not** been made of record. As such, the Examiner will comment thereon.

The Examiner will accept that drug-drug interactions of varying consequences have been known in the art. Indeed, as could be gleaned from any textbook or other comprehensive reference on drugs and their actions, contraindications and possible side effects are common in the medical arts. In the face thereof, and possibly in the face of other disclosures of combinations of drugs providing a greater-than-additive or synergistic results, there still remains

the successful, ongoing act of administering combinations of active agents with known side effects and possible drug interactions for the purpose of treating individuals in need of therapy. It would have been well within the skill of the art to be cognizant of such possibilities and to cautiously proceed with the therapy indicated.

Quite simply, the Examiner does not accept that just because side effects or drug interactions were possible or known for a number of given drugs or combinations of drugs, it then must follow, or then most likely follows that one of ordinary skill in the art, interested in the successful treatment of diabetic neuropathy and having knowledge of such possible or known drug-drug interactions, would have, more times than not, a less than reasonable expectation of success in practicing a therapy against diabetic neuropathy comprising the administration of a combination of drugs for which there is no teaching of adverse effects or drug-drug interactions.

In present case, given that which was known in the art concerning the presently claimed subject matter, it is believed that, contrary to Appellants' position, such subject matter would have been obvious and that the artisan would have been imbued with at least a reasonable expectation of success in practicing the combination therapy for diabetic neuropathy as presently claimed and as suggested by the art. It is further noted that Appellants have not offered any showing related to inhibiting cGMP PDE5 or to therapies known for the treatment of diabetic neuropathies which would have led to a lack of a reasonable expectation in administering the a combination of the claimed actives for treating diabetic neuropathy.

On the record, the Examiner has taken the position that Yamasaki et al. support the conclusion that the presently claimed combination would have been obvious to one of ordinary skill in the art because the patentees disclose "different" benzimidazole compounds for treating

diabetic neuropathy. However, as correctly pointed out by Appellants, "the Examiner does not state that the compounds are used in combination with each other as stated in Appellants' claims", (brief at page 19, first full paragraph). Therefor, the Examiner will withdraw these comments and no longer adhere to them. Nevertheless, the remaining findings of fact clearly support the Examiner's position on the obviousness of the claimed subject matter.

Appellants' have taken issue with the Examiner's statement that the function of (i) gabapentin and/or pregabalin and (ii) the benzimidazoles of Yamasaki et al. have a common function, (brief at page 19, lines 4+ following the quoted subject matter). Appellants believe this to be not true because the former are alpha 2 delta ligands and the latter, cGMP PDE5 inhibitors. The Examiner did not represent that a common mechanism of action was present, but rather a common function, i.e., the treatment of diabetic neuropathy. Also, contrary to Appellants further remarks, that the mechanisms of action are not the same, (e.g., such as with sildenafil and the benzimidazoles of Yamasaki et al.), does not diminish the propriety of the present rejection because this circumstance does not mean that one of ordinary skill in the art would not have been motivated to combine two compounds, each of which was known for the treatment of diabetic neuropathy, for the treatment of such neuropathy. The expectation would be one based on at least an expectation of additive results and it has not been demonstrated on the record that Appellants' combination produces any results that would not have been expected.

Appellants' further their opinion that drugs having different mechanisms of action would not have been combined by setting forth that such a combination "may" have a drug-drug interaction , (brief, sentence bridging pages 19-20). Hypotheticals, however, simply do not serve the place of an actual contraindication to a particular combination of active agents. That is, the

possibility that the presently claimed combination of actives could have dangerous effects is not sufficient. The Examiner could equally take the position, and support such a position with a significant number of examples, in both the patent and non-patent literature, where drug combinations are taught and which have a favorable benefit-to-risk profile. In an effort not to crowd the present record with such references readily available to those having an interest therein, such references have not been cited by the Examiner. Therefore, for the above reasons this point of Applicants cannot be afforded the significance urged.

Appellants have also taken issue with the above position by the Examiner, (brief, page 20, second full paragraph). Appellants state that the burden is not on them to demonstrate an actual contraindication to the particular combination of active agents and that they have raised a sufficient question regarding the expectation of success as did the Examiner above when referring to examples in the literature where combinations of actives having different mechanisms of action are present. While the Examiner will agree that the presentation of a direct contraindication against the specifically claimed actives is not required, it is nevertheless believed that the teachings relied on by Appellants are just not sufficient to overcome the present conclusion of obviousness.

Finally, respecting present claims 21 and 32, Appellants have asserted that the subject matter defined thereby would not have been obvious because nothing in the art cited, (Ellis et al.), would have motivated one to select the particular compound sildenafil from among all the cGMP PDE5 inhibitors disclosed. The Examiner stands on his findings that Yamasaki et al. teach that cGMP PDE5 inhibitors are effective for the treatment of diabetic neuropathy and because sildenafil was a known cGMP PDE5 inhibitor, it would have been obvious to have used

it as the inhibitor or with the inhibitors of Yamasaki et al. as well as with gabapentin and/or pregabalin

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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